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Electrocardiographic disturbances in children with systemic lupus erythematosus

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ABSTRACT

Background: Conduction disturbances other than heart block related to neonatal lupus are rarely explored and reported in children with systemic lupus erythematosus (SLE).
Objective: To report the electrocardiographic (ECG) abnormalities in children with SLE and assess whether anti-Ro/SSA antibodies and hydroxychloroquine are associated with the rhythm disturbances.
Methods: This cross-sectional retrospective study comprised patients with SLE who had regular follow-up in the Pediatric Lupus Clinic at King Faisal Specialist Hospital and Research Center-Riyadh. All enrolled patients were evaluated with regard to demographics, age at disease onset, disease duration, clinical and laboratory variables including autoantibodies, disease activity using SLEDAI disease activity index, and medications. An expert pediatric cardiologist reviewed the ECG findings of all enrolled patients independently without knowing the clinical status of the patients.
Results: A total of 41 (35 females, 6 males) unselected patients with SLE with a mean age of 12.8 (2.5) years and mean follow-up duration of 4 (3) years completed the evaluation. The most frequent manifestations were renal disease (65.8%), followed by musculoskeletal (46.3%), hematological (41.5%), and cardiac involvement (19.5%). Thirty-two had active disease (SLEDAI >4), and the mean of SLEDAI was 9.2 (6.2). ECG abnormalities were seen in 12 patients (29.3%); these changes included ST-T changes (9.8%), right bundle branch block (7.3%), 4 prolonged QT interval (9.8%), and low QRS voltage (2.4%). Thirty-seven (90.3%) patients were on hydroxychloroquine, and 9 patients (22%) had positive anti-Ro/SSA antibodies. ECG abnormalities were associated significantly with anti-Ro/SSA antibodies ($P < .05$) and a low platelet count ($P < .5$) but had no association with other autoantibodies, hydroxychloroquine, or SLEDAI score.
Conclusion: Children with SLE with anti-Ro/SSA antibodies are probably prone to heart conduction abnormalities. However, the heart rate and QT interval were affected by hydroxychloroquine. A larger prospective study is required to allow more definitive conclusions.

1. Introduction

Childhood systemic lupus erythematosus (cSLE) is a complex systemic inflammatory disease that runs a chronic, unpredictable, relapsing remitting course that may compromise the multisystem including the cardiac structures [1,2]. Despite the similarity with the adult counterpart, cSLE tends to be more severe with more organ involvement and laboratory abnormalities [3]. Cardiac involvement is one of the frequent manifestations in SLE [4]. Pericarditis is the most common feature, but other rarer manifestations including myocarditis, endocarditis, coronary artery diseases, and conduction disturbances may occur [5–7]. The electrocardiographic (ECG) abnormalities including rhythm and conduction disturbances such as bundle branch block (BBB) and atrioventricular block are probably more frequent in SLE than in the general population because of the disease and other comorbidities. Therefore, cardiovascular system sequelae are recognized as critical, particularly in adult patients with SLE [7,8]. In contrast, conduction disturbances other than heart block related to neonatal

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lupus are rarely investigated and reported in children with SLE.

The definite cause of the conduction disturbances in SLE remains not well understood. Myocarditis either symptomatic or subclinical seems to be one of the main pathophysiological mechanisms in adult patients. However, the possible association of conduction disturbances and autoantibodies such as anti-Ro/SSA and antiphospholipid antibodies with cardiac toxicity secondary to antimalarial drugs remains controversial [9–11]. Because no data were available for cSLE, we reported the ECG abnormalities in patients with cSLE and assessed the association between anti-Ro/SSA antibodies and hydroxychloroquine and ECG abnormalities.

2. Methods

This is a cross-sectional retrospective analysis of prospectively collected data. The present analysis includes patients with cSLE who were undergoing treatment and regular follow-up in our Pediatric Lupus Clinic at King Faisal Specialist Hospital and Research Center (KFSHRC), Riyadh. All included patients fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) criteria and the diagnosis made before the age of 14 years [12].

As part of our health care assessment of patients with SLE, all patients completed the cardiac evaluation, including resting standard 12-lead ECG and echocardiography during their follow-up. All enrolled patients were evaluated at a single visit with regard to demographics: age at disease onset, disease duration,clinical and laboratory variables, including autoantibodies, especially anti-Ro/SSA, anti-La/SSB, and antiphospholipid antibodies. Medication, particularly hydroxychloroquine, within the follow-up period was reviewed. Additionally, disease activity was assessed using SLE disease activity index (SLEDAI) [13]. Furthermore, an expert pediatric cardiologist specialized in electrophysiology (WM) reviewed the 12-lead ECGs of all enrolled patients independently without knowing the clinical status of the patients for the rhythm, conduction disturbance, ST-T changes, and QT intervals. The following definitions of ECG abnormalities were considered: QRS width, more than 100 ms; prolonged QT interval, more than 450 ms; ST-segment elevation or depression, more than 0.1 mV/1 mm.

Disease activity, hydroxychloroquine use, and anti-SSA/Ro and antiphospholipid antibodies positivity before the ECG were studied as potential factors associated with ECG abnormalities.

All collected data were analyzed under confidentiality practice and no personal identity needed. All clinical and laboratory assessments were a result of routine medical care, and informed consent was taken at the time of the renal biopsy. The study was conducted in accordance with the ethical principles contained in the Declaration of Helsinki (2000) and guidelines of the Research Advisory Council (RAC) of the KFSHRC and the laws of Saudi Arabia. It was approved under the reference RAC# 2161236.

2.1. Statistical methods

Results are expressed as mean, SD for continuous variables, and categorical variables are reported as frequencies and percentages. Student's independent *t*-test or ANOVA was used as appropriate to compare the mean values of the variables. We used univariate analysis to study the effects of hydroxychloroquine use and autoantibodies on the ECG abnormalities. Statistical significance was defined as a P value of $< .05$.

3. Results

Forty-one patients with cSLE were included, of whom 35 were female and six were male. The mean age of the patients was 12.8 (2.5) years, and the mean disease duration was 4.1 (3) years. At the time of the ECG assessment, 37 patients were treated with hydroxychloroquine with a daily dose of 6 mg/kg, but four patients did not receive it because three of them were glucose-6-phosphate dehydrogenase deficient and one patient had a familial retinal disease. Most of the patients had renal involvement (65.9%) followed by musculoskeletal manifestations (46.3%) and hematological involvement (41.5%). Eight patients had cardiac involvement, of which four of them had pericarditis with effusion, two patients had mitral valve regurgitation, and the remaining two patients had cardiomyopathy. Additionally, 12 patients had high blood pressure and hence required antihypertensive medications. Table 1 shows the demographic features and the frequency of clinical features with SLEADI score.

Thirty-two patients had active disease, and the mean SLEDAI was 9.2 (6.2). Elevated levels of anti-Ro/SSA and anti-La/SSB antibodies were detected in 16 and 9 patients, respectively, whereas antiphospholipid antibodies were found in 19 patients (10 patients with β2-glycoprotein and 9 patients with IgG anticardiolipin). All patients had normal electrolyte levels, especially calcium, magnesium, and potassium.

Twelve patients (29.2%) had abnormal ECG findings. Table 2 shows the proportions of patients with various ECG changes. Four patients had prolonged QT interval (>450 ms) and three patients showed incomplete right BBB, with RsR and widening QRS (>100 ms). Nonspecific ST-T segment in at least six leads was noticed in four patients, while one patient had low QRS voltage. Of the eight patients with SLE-related cardiac involvement, only three patients showed ECG changes, two of them showed ST-segment changes, one had findings compatible with myocardial infarction, one patient showed nonspecific changes, and one had a right BBB.

No association of hydroxychloroquine use and disease activity (SLEDAI) with ECG abnormalities was observed in our cohort. However, the presence of anti-Ro/SSA antibodies associated significantly with ECG abnormalities but no significant association with a specific individual ECG abnormality. Eight of the 16 patients with positive anti-Ro/SSA antibodies had abnormal ECG findings, while only four of the 25 patients with negative anti-Ro/SSA had ECG abnormalities ($P < .05$), but anti-SSB/La antibodies and

Table 1
Demographic features and the frequency of pertinent clinical and laboratory findings with SLEADI score.

Feature	Frequency (%)
Female	85.4
Age (mean, SD)	12.8, 2.5
Age at onset (mean, SD)	8.6, 3.4
Age at diagnosis (mean, SD)	8.8, 3.4
Disease duration (mean, SD)	4.1, 3.0
Duration of follow-up (mean, SD)	4.0, 3.0
Mucocutaneous	36.6
Nephritis	65.9
Musculoskeletal	46.3
Hematological	41.5
Cardiac	19.5
Autoantibodies	
Anti-Ro/SSA	16 (39)
Anti-La/SSB	9 (21.9)
Anti-Smith	17 (41.7)
β2-Glycoprotein IgG	10 (24.4)
Anticardiolipin IgG	9 (21.9)
SLEDAI (mean, SD)	9.2, 6.2
Medications	
Corticosteroids	20 (48.8)
Hydroxychloroquine	37 (90.2)
Immunosuppressants	28 (68.3)
Aspirin	6 (14.6)
Antihypertensive	12 (29.3)

SLEDAI, systemic lupus erythematosus disease activity index.

antiphospholipid (both beta-2-glycoprotein and IgG anti-cardiolipin) antibodies had no association with ECG abnormalities. No additional variables were significantly associated with ECG abnormalities, but low platelet count showed a significant association ($P < .05$).

4. Discussion

The range of cardiac involvement in patients with cSLE includes frequent clinical features that occur as a consequence of active disease such as pericarditis and less frequent but serious manifestations that are secondary to disease damage [4,14]. However, silent cardiac involvement in the form of conduction disturbances without overt clinical cardiac disease has been described [7]. The prevalence of ECG abnormalities in adult patients with SLE, including prolonged QT interval, ST-T segment changes, conduction disturbances, and arrhythmias, appears to be higher than that in the general population [9,10,15]. Recently, ECG abnormalities and certain factors, namely, anti-Ro/SSA and hydroxychloroquine use, potentially responsible for causing these abnormalities gained increased attention in adult patients with SLE but with conflicting results [9,10].

Several studies have examined cardiac involvement in cSLE, and most of these reports focused on the clinical manifestations [14,16–19]. Cardiac manifestations, particularly pericarditis and pericardial effusion, are common and usually occurred at the time of diagnosis or within six months. However, asymptomatic cardiac involvement such as ECG abnormalities, trivial valvular lesions, and subclinical ventricular dysfunction is frequently detected in patients with cSLE [14,20,21]. The ECG abnormalities usually reported scattered with other cardiac manifestations; thus, these abnormalities including nonspecific ST-T segment changes, left axis deviation, arrhythmia, and conduction disturbances did not gain enough attention in cSLE. To the best of our knowledge, no studies reported on the prevalence of the ECG abnormalities. With the exception of one report, there was no mention of the association of anti-Ro/SSA or hydroxychloroquine use with cardiac involvement in cSLE. Furthermore, that report identified a correlation of anti-Ro/SSA and anti-La/SSB with pericarditis and myocarditis but without mentioning ECG abnormalities [16]. Therefore, to better understand the spectrum of ECG abnormalities in cSLE, we examined the ECG records of 41 patients with cSLE and specifically assessed the association of anti-Ro/SSA antibodies and hydroxychloroquine use with ECG abnormalities. The frequency of ECG abnormalities in our cohort was considerably high. The abnormalities related to conduction defects manifested as prolonged QT interval (9.8%) and BBB (7.3%), while abnormalities that may represent sequelae of myocardial instability were seen in 9.8% of patients. Our study demonstrated an important association between ECG abnormalities, particularly prolonged QT and anti-Ro/SSA antibodies. Studies that evaluated adult patients with SLE identified a similar association between anti-Ro/SSA and QT interval prolongation [9,22]. However, our results did not show a significant association between other autoantibodies, especially anti-La/SSB and antiphospholipid, and ECG abnormalities.

Table 2
Proportions of patients with various electrocardiographic abnormalities.

ECG findings	Frequency (%)
Prolonged QT interval	4 (9.8)
RBBB	3 (7.3)
ST-T segment changes	4 (9.8)
Low QRS voltage	1 (2.4)
Normal	29 (70.7)

ECG, electrocardiographic; RBBB, right bundle branch block.

Anti-Ro/SSA is a well-known trigger of heart block in neonatal lupus because of the cross-reaction of maternal IgG anti-Ro/SSA antibodies with immature cardiomyocytes of the fetal conductive system, thereby causing irreversible conduction damage [23]. Although the exact pathogenesis in the population beyond the infancy period is not fully understood, an increasing evidence suggests that anti-Ro/SSA antibodies may induce cardiomyocyte injury, thus leading to arrhythmias in children and adults with SLE [10,22].

Studies from adult patients with SLE linking ECG abnormalities to hydroxychloroquine use showed conflicting results [10,24]. Our data did not show that ECG abnormalities attributed to hydroxychloroquine use. Hydroxychloroquine is an important drug and is widely used in the management of SLE. Furthermore, hydroxychloroquine-related cardiac manifestations, namely, conductive disorders, remain rare and unpredictable.

Regarding limitations, our study is a small sample and lacks a comparison group. Additionally, it was limited by a single ECG assessment.

In conclusion, our results showed that children with SLE with anti-Ro/SSA antibodies are probably prone to heart conduction abnormalities. However, the heart rate and QT interval were affected by hydroxychloroquine use. A larger prospective study is required to allow more definitive conclusions.

Conflicts of interest

Authors have nothing related to this work to be disclosed.

Please note that this work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical statement

The study was conducted in accordance with the ethical principles and guidelines of the Research Advisory Council of our institution. It was approved under the reference of RAC# 2161236.

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